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(54) Title: THERAPEUTIC COMBINATIONS OF (SELECTIVE) ESTROGEN RECEPTOR MODULATORS (SERM) AND GROWTH HORMONE SECRETAGOGUES (GHS) FOR TREATING MUSCULOSKELETAL FRAILTY

(57) Abstract

This invention is directed to pharmaceutical combination compositions and methods comprising (–)–cis–6– phenyl–5–(4– (2–pyrrolidin–1– yl–ethoxy) –phenyl)– 5,6,7,8– tetrahydronaphthalene –2–ol or a pharmaceutically acceptable salt thereof and 2–amino–N–(1(R) –(2,4–difluoro– benzyloxymethyl) –2–oxo–2–(3– oxo–3a(R) –pyridin–2– ylmethyl)–2–(2,2,2–trifluoro–ethyl) –2,3,3a,4,6,7 –hexahydro –pyrazolo [4,3–c]pyridin –5–yl)–ethyl) –2–methyl–propionamide or a pharmaceutically acceptable salt thereof, methods of using such compositions and kits containing such compositions. The compositions are useful for treating musculoskeletal frailty, including osteoporosis, osteoporotic fracture, low bone mass, frailty and low muscle mass.

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THERAPEUTIC COMBINATIONS OF (SELECTIVE) ESTROGEN RECEPTOR MODULATORS (SERM) AND GROWTH HORMONE SECRETAGOGUES (GHS) FOR TREATING MUSCULOSKELETAL FRAILTY

BACKGROUND OF THE INVENTION

This invention relates to a pharmaceutical combination of a selective estrogen receptor modulator (SERM) and a growth hormone secretagogue (GHS) that stimulates bone formation, increases bone mass, decreases serum lipid levels and increases muscle mass. The invention also relates to kits containing such combinations and the use of such combinations to treat musculoskeletal frailty, including osteoporosis, osteoporotic fracture, low bone mass, frailty, low muscle mass and the like in mammals, including humans. In particular, this invention relates to a combination of (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof, kits containing such a combination and the use of such a combination to treat musculoskeletal frailty, including osteoporosis, osteoporotic fracture, low bone mass, frailty, low muscle mass and the like in mammals, including humans.

Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated.

The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecast to increase three-fold over the next 60 years, and one study estimates that there will be 4.5 million hip fractures worldwide in 2050.

Although both men and women are susceptible to musculoskeletal frailty, including osteoporosis, women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss immediately following

menopause. Other factors that increase bone loss leading to osteoporosis include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

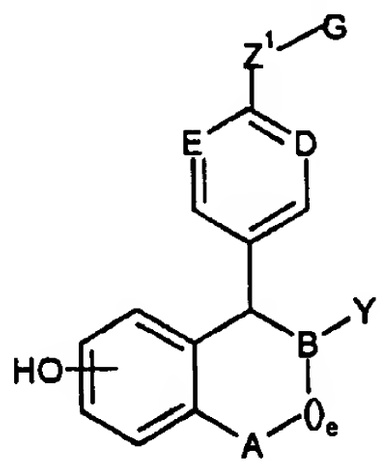
Estrogen is the agent of choice in preventing osteoporosis or post menopausal bone loss in women. In addition, Black, et al. in EP 0605193A1 report that estrogen, particularly when taken orally, lowers plasma levels of LDL and raises those of the beneficial high density lipoproteins (HDL's). Long-term estrogen therapy, however, has been implicated in a variety of disorders, including an increase in the risk of uterine cancer, endometrial cancer and possibly breast cancer, causing many women to either avoid this treatment or take the medication for only a short period of time. Although the risk of endometrial cancer is thought to be reduced by a concurrent use of a progesterone, there is still concern about possible increased risk of breast cancer with the use of estrogen. Recently suggested therapeutic regimens, which seek to lessen the cancer risk, such as administering combinations of progesterone and estrogen, cause the patient to experience unacceptable bleeding. Furthermore, combining progesterone with estrogen seems to blunt the serum cholesterol lowering effects of estrogen. The significant undesirable side effects associated with estrogen therapy support the need to develop alternative therapies for osteoporosis that have the desirable beneficial effect on serum LDL but do not cause undesirable side effects.

Recently, a number of selective estrogen receptor modulators have been proposed for treatment of osteoporosis. It has been reported (Osteoporosis Conference Scrip No. 1812/13 April 16/20, 1993, p. 29) that raloxifene, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy) benzoyl] benzo[b] thiophene, mimics the favorable action of estrogen on bone and lipids but, unlike estrogen, has minimal uterine stimulatory effect. [Black, L.J. et al., Raloxifene (LY139481 Hcl) Prevents Bone Loss and Reduces Serum Cholesterol Without Causing Uterine Hypertrophy in Ovariectomized Rats, J. Clin. Invest., 1994, 93:63-69 and Delmas, P.D. et al., Effects of Raloxifene on Bone Mineral Density, Serum Cholesterol Concentration, and Uterine Endometrium in Postmenopausal Women, New England Journal of Medicine, 1997, 337:1641-1647].

Agents such as droloxifene, U.S. pat. no. 5,254,595, prevent bone loss and thereby reduce the risk of fracture without estrogen's side effects. However, estrogen and estrogen agonists alone are only expected to reduce the fracture risk

by about 50% leaving approximately 50% of osteopenic women still at risk for an osteoporotic fracture.

Commonly assigned U.S. pat. no. 5,552,412, which is incorporated herein by reference, discloses SERM compounds of the formula



wherein the variables are defined as set forth therein.

Growth hormone (GH), which is secreted from the pituitary gland, stimulates growth of all tissues of the body that are capable of growing. In addition, GH is known to have the following basic effects on the metabolic process of the body:

1. Increased rate of protein synthesis in substantially all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

Deficiency in GH results in a variety of medical disorders. In children, it causes dwarfism. In adults, the consequences of acquired GH deficiency include profound reduction in lean body mass and concomitant increase in total body fat, particularly in the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to a significant reduction in exercise capacity. Bone density is also reduced. Administration of exogenous GH has been shown to reverse many of the metabolic changes. Additional benefits of therapy have included reduction in LDL cholesterol and improved psychological well-being.

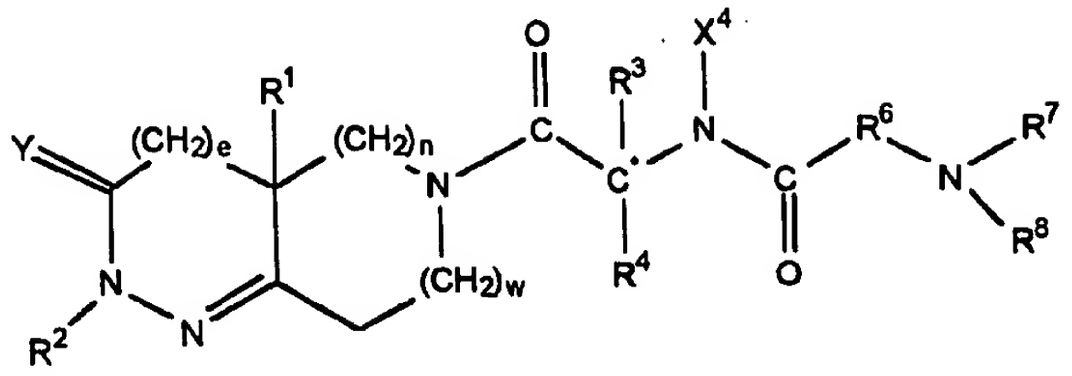
In cases where increased levels of GH were desired, the problem was generally solved by providing exogenous GH or by administering an agent which stimulated GH production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of

GH was the extraction of the pituitary glands of cadavers. This resulted in an expensive product, and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the GH (e.g., Jacob-Creutzfeld disease). Recently, recombinant GH has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Most GH deficiencies are caused by defects in GH release, not primary defects in pituitary synthesis of GH. Therefore, an alternative strategy for normalizing serum GH levels is by stimulating its release from somatotrophs. Increasing GH secretion can be achieved by stimulating or inhibiting various neurotransmitter systems in the brain and hypothalamus. As a result, the development of synthetic GH-releasing agents to stimulate pituitary GH secretion are being pursued, and may have several advantages over expensive and inconvenient GH replacement therapy. By acting along physiologic regulatory pathways, the most desirable agents would stimulate pulsatile GH secretion, and excessive levels of GH that have been associated with the undesirable side effects of exogenous GH administration would be avoided by virtue of intact negative feedback loops.

Physiologic and pharmacologic stimulators of GH secretion include arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause GH to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue GH releasing factor (GHRF) or an unknown endogenous GH-releasing hormone or all of these.

Commonly assigned International Patent Application Publication Number WO97/24369, designating, *inter alia*, the U.S., discloses GH secretagogues of the formula



wherein the variables are defined as set forth therein. International Patent Application Publication Number WO97/24369 is incorporated herein by reference.

Tang et al., Restoring and Maintaining Bone in Osteogenic Female Rat Skeleton: I. Changes in Bone Mass and Structure, J. Bone Mineral Research 7 (9), p1093-1104, 1992 discloses data for the lose, restore and maintain (LRM) concept, a practical approach for reversing existing osteoporosis. The LRM concept uses anabolic agents to restore bone mass and architecture (+ phase) and then switches to an agent with the established ability to maintain bone mass, to keep the new bone (+/- phase). The rat study utilized PGE_2 and risedronate, a bisphosphonate, to show that most of the new cancellous and cortical bone induced by PGE_2 can be maintained for at least 60 days after discontinuing PGE_2 by administering risedronate.

Shen et al., Effects of Reciprocal Treatment with Estrogen and Estrogen plus Parathyroid Hormone on Bone Structure and Strength in Ovariectomized Rats, J. Clinical Investigation, 1995, 96:2331-2338 discloses data for the combination and/or sequential use of anti-resorptive agents and anabolic agents for the treatment of osteoporosis.

Commonly assigned International Patent Application Publication Number WO97/31640, designating, *Inter alia*, the U.S., discloses the use of certain GH secretagogues in combination with certain SERMS to treat osteoporosis. International Patent Application Publication Number WO97/31640 is incorporated herein by reference.

SUMMARY OF THE INVENTION

This invention is directed to a pharmaceutical composition comprising:

a. a first compound, said first compound being (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof; and

b. a second compound, said second compound being 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof.

This invention is further directed to a pharmaceutical composition as recited in the immediately preceding paragraph additionally comprising a pharmaceutical carrier.

This invention is still further directed to a composition as set forth in either of the first two paragraphs of this summary wherein said first compound is (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol D-tartrate and said second compound is 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate.

This invention is still further directed to a method, designated Method A, for treating a mammal suffering from musculoskeletal frailty comprising administering to said mammal a pharmaceutical composition as recited in any of the first three paragraphs of this summary.

A preferred method within Method A, designated Method B, is wherein said mammal is suffering from osteoporosis.

Another preferred method within Method A, designated Method C, is wherein said mammal is suffering from osteotomy, childhood idiopathic bone loss or bone loss associated with periodontitis.

This invention is still further directed to a method, designated Method A^1, for treating a mammal suffering from musculoskeletal frailty comprising administering to said mammal

a. a first compound, said first compound being (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof; and

b. a second compound, said second compound being 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof.

This invention is particularly directed to a method of Method A^1 wherein the first compound and the second compounds are administered substantially simultaneously.

This invention is also particularly directed to a method of Method A^1, hereinafter termed Method D, wherein the second compound is administered for a period of from about three months to about three years.

This invention is more particularly directed to a method of Method D followed by administration of the first compound for a period of from about three months to about three years without the administration of the second compound during the period of from about three months to about three years.

This invention is also more particularly directed to a method of Method D followed by administration of the first compound for a period greater than about three years without the administration of the second compound during the greater than about three year period.

This invention is also directed to a method, hereinafter termed Method E, for treating a mammal suffering from musculoskeletal frailty comprising administering to said mammal a therapeutically effective amount of a composition as recited in any of the first threee paragraphs of this summary.

A preferred method within Method E is wherein bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction is enhanced, vertebral synostosis is induced, long bone extension is enhanced, the healing rate of a bone graft or a long bone fracture is enhanced or prosthetic ingrowth is enhanced.

This invention is also directed to a method for increasing muscle mass in a mammal comprising administering to said mammal a muscle mass increasing effective amount of a composition as recited in any of the first three paragraphs of this summary.

In all of the methods of this invention, it is particularly preferred that the mammal is a human.

This invention is also directed to a kit comprising a treatment for a mammal suffering from musculoskeletal frailty comprising:

a. (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier in a first unit dosage form;

b. 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier in a second unit dosage form; and

c. a container.

This invention is particularly directed to a kit as described in the immediately preceding paragraph wherein said first unit dosage form comprises (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol D-tartrate and said second unit dosage form comprises 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate.

In all of the compositions, methods and kits of this invention, it is particularly preferred that the D-tartrate salt of (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol is used and that the L-tartrate salt of 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide is used.

The phrase "condition which presents with low bone mass" refers to a condition where the level of bone mass is below the age specific normal as defined in standards by the World Health Organization "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis (1994), Report of a World Health Organization Study Group. World Health Organization Technical Series 843". Childhood idiopathic and primary osteoporosis are also included. Included in the treatment of osteoporosis is the prevention or attenuation of long term complications such as curvature of the spine, loss of height, prosthetic surgery, and prevention of prostate malfunctioning. Also included is increasing the bone fracture healing rate and enhancing the rate of

successful bone grafts. Also included is periodontal disease and alveolar bone loss.

The phrase "condition which presents with low bone mass" also refers to a mammal known to have a significantly higher than average chance of developing such diseases as are described above including osteoporosis (e.g., post-menopausal women, men over the age of 60, and persons being treated with drugs known to cause osteoporosis as a side effect (such as glucocorticoid)).

Those skilled in the art will recognize that the term bone mass actually refers to bone mass per unit area which is sometimes (although not strictly correctly) referred to as bone mineral density.

The phrase "musculoskeletal frailty" refers to a condition wherein a subject has low bone mass and/or low muscle mass, and includes such diseases, disorders and conditions such as, but not limited to, conditions which present with low bone mass, osteoporosis, conditions which present with low muscle mass, osteotomy, childhood idiopathic bone loss, bone loss associated with periodontitis, bone healing following facial reconstruction, maxillary reconstruction, mandibular reconstruction and bone fracture. Further, musculoskeletal frailty encompasses such conditions as interfaces between newly attached prostheses and bone which require bone ingrowth.

The term "treating", "treat" or "treatment" as used herein includes curative, preventative (e.g., prophylactic) and palliative treatment.

The parenthetical negative or positive sign used herein in the nomenclature denotes the direction plane polarized light is rotated by the particular stereoisomer.

The compositions of this invention may include hydrates of the compounds used therein.

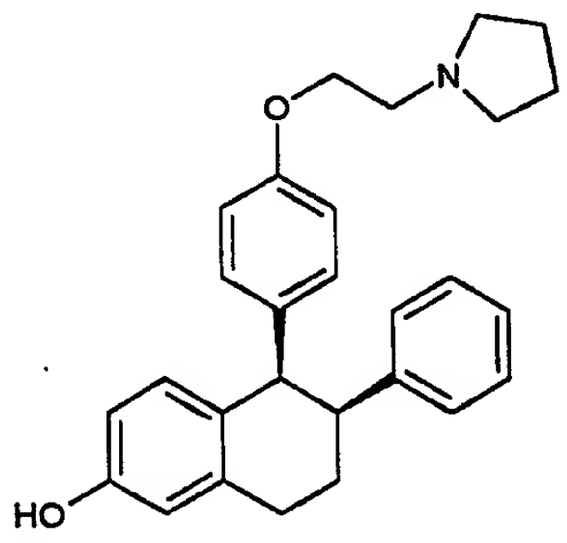
The pharmaceutical compositions and methods of this invention result in a more rapid and higher magnitude bone mass gain than is achievable with the same doses of (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol as described above alone or 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide as described above alone. Thus, these combinations increase bone mass and decrease fracture rates to a greater extent than is achievable through

use of either agent alone. Further, these combinations increase bone density and muscle mass while at the same time reducing fat mass and total serum cholesterol. This invention makes a significant contribution to the art by providing compositions and methods that increase and maintain bone mass resulting in prevention, retardation, and/or regression of osteoporosis and related bone disorders.

Other features and advantages will be apparent from the specification and claims which describe the invention.

DETAILED DESCRIPTION OF THE INVENTION

The first compound of this invention is (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, or a pharmaceutically acceptable salt thereof, which has the structure of Formula I:



I

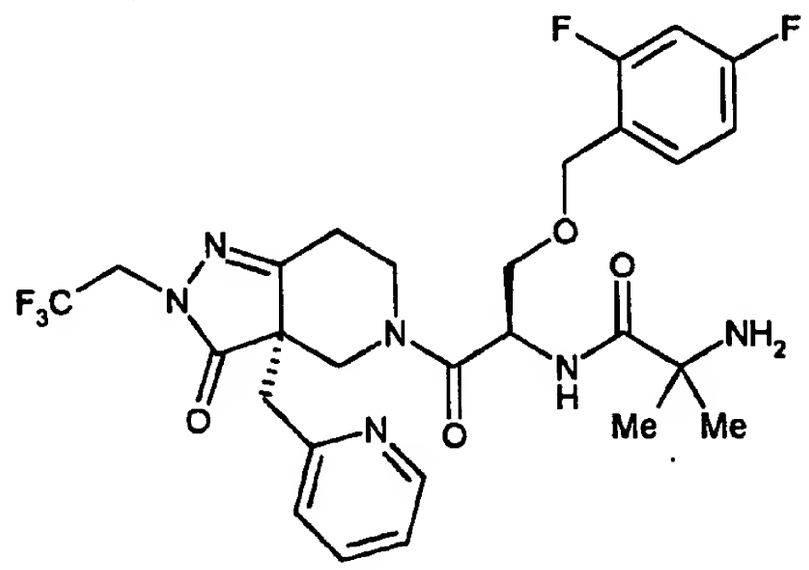
(-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol and the pharmaceutically acceptable salts thereof are prepared as described in commonly assigned US Patent Number 5,552,412, which is referenced above.

(-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol D-tartrate is prepared as set forth in the immediately preceding paragraph or, alternatively, as set forth in International Patent Application Publication Number WO97/16434, designating the United States and which is incorporated herein by reference.

The second compound of this invention is 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-

[redacted]

2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof, which has the structure of Formula II:



II

2-Amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide and the pharmaceutically acceptable salts thereof are prepared as set forth in commonly assigned International Patent Application Publication Number WO97/24369, designating, *inter alia,* the United States, which is referenced above.

2-Amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate is prepared as set forth in International Patent Application Publication Number WO97/24369, referenced above. Alternatively, 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate is prepared as described in Example One herein.

In addition, when the compounds and pharmaceutically acceptable salts thereof used in the compositions and methods of this invention form hydrates or solvates such hydrates or solvates are also within the scope of the invention.

The pharmaceutical combinations and methods of this invention are all adapted to therapeutic use as agents that either activate bone turnover or prevent bone resorption or increase bone formation in mammals, particularly humans.

Since these functions are closely related to the development of osteoporosis and bone related disorders, these combinations, by virtue of their action on bone, prevent, arrest, regress or reverse osteoporosis.

The utility of the compositions and methods of the present invention as medical agents in the treatment of musculoskeletal frailty (e.g., conditions which present with low bone mass or low muscle mass including osteoporosis) in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in conventional assays as set forth in U.S. Patent Number 5,552,412 and International Patent Application Publication Number WO97/24369. Further evidence of the utility of the instant combination is set forth in Example Two below. Such assays also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

Administration of the compounds of this invention can be via any method which delivers a compound of the combination of this invention systemically and/or locally. These methods include oral routes, parenteral, intraduodenal routes, etc. Generally, the compounds of this invention are administered orally, but parenteral administration (e.g., intravenous, intramuscular, transcutaneous, subcutaneous or intramedullary) may be utilized, for example, where oral administration is inappropriate for the instant target or where the patient is unable to ingest the drug. The two different compounds of this invention can be co-administered simultaneously or sequentially in any order, or a single pharmaceutical composition comprising a first compound as described above and a second compound as described above in a pharmaceutically acceptable carrier can be administered.

In any event the amount and timing of compounds administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgment of the prescribing physician. Thus, because of patient to patient variability, the dosages given below are a guideline and the physician may titrate doses of the drug to achieve the activity (e.g., bone mass augmentation) that the physician considers appropriate for the

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individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as bone mass starting level, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular). For example, the administration of (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol can provide cardiovascular benefits, particularly for post-menopausal women. The following paragraphs provide preferred dosage ranges for the various components of this invention.

An effective dosage for (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol is in the range of 0.0001 to 100 mg/kg/day, preferably 0.001 to 10 mg/kg/day.

An effective dosage for 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide is in the range of 0.0001 to 100 mg/kg/day, preferably 0.01 to 5 mg/kg/day.

Where the tartrate salt or other pharmaceutically acceptable salt of either of the above compounds is used in this invention, the skilled person will be able to calculate effective dosage amounts by calculating the molecular weight of the salt form and performing simple stoichiometric ratios.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds or pharmaceutically acceptable salts thereof of this invention together with a pharmaceutically acceptable carrier or diluent. Thus, the compounds and pharmaceutically acceptable salts thereof of this invention can be administered separately or together in any conventional oral, parenteral or transdermal dosage form. When administered separately, the administration of the other compound or pharmaceutically acceptable salt thereof of the invention follows.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia.

Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds or pharmaceutically acceptable salts thereof of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g.,topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of each active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1990).

Pharmaceutical compositions according to the invention may contain 0.1%-95% of a combination of the compounds or pharmaceutically acceptable salts thereof of this invention, preferably 1%-70%. In any event, the composition or formulation to be administered will contain a quantity of the compounds or pharmaceutically acceptable salts thereof of the invention in an amount effective to treat the disease/condition of the subject being treated.

Since the present invention relates to treatment with a combination of the two active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit includes two separate pharmaceutical compositions: (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof and 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof. The kit includes a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It is desirable to provide a memory aid on a card insert, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the

days of the regimen which the tablets or capsules so specified should be ingest d. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also a daily dose of SERM can consist of one tablet or capsule while a daily dose of a GH secretagogue can consist of several tablets or capsules. The memory aid should reflect this.

In another specific embodiment of the invention a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

Example 1

2-Amino-N-{1-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide L-(+) tartrate

A. 4-Oxo-3-pyridin-2-ylmethyl-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-ethyl ester

To a solution of 4-oxo-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-ethyl ester (10.34 g, 38.2 mmol) in DMF (40 mL) at about 0 °C was added picolyl chloride hydrochloride (5.7 g, 34.7 mmol), potassium carbonate (14.4 g, 104.1 mmol) and potassium iodide (5.76 g, 34.7 mmol). After stirring at about 0 °C for about 2 hours, the ice bath was removed and DABCO (973 mg, 8.68 mmol) was added. The reaction mixture was stirred for about 30 min. and poured into a mixture of water and IPE. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was crystallized from hexanes to give a white solid (8.19 g, yield 65%). ^{1}H-NMR ($CDCl_3$) δ 1.17 (t, 3H), 1.48 (s, 9H), 1.55

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(s, 2H), 2.61 (m, 1H), 2.71 (m, 1H), 3.31-3.50 (m, 3H), 4.11 (d, 2H), 4.49 (d, 1H), 7.06 (br s, 1H), 7.17(d, 1H), 7.54 (m, 1H), 8.40 (s, 1H).

B. 3-Oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester

A 70% aqueous solution of $CF_3CH_2NHNH_2$ (325 mL, 1.986 mol) (obtained from Aldrich) was extracted with toluene (3 x 1200 mL). To a solution of the product made according to step A (600 g, 1.655 mol) in toluene (900 mL) was first added the combined toluene extracts containing the anhydrous 2,2,2-trifluoroethyl hydrazine, followed by acetic acid (121.4 g, 1.986 mol). The reaction mixture was heated at about 70 °C for about 2 hours , then another toluene extraction of 70% aqueous 2,2,2-trifluoroethyl hydrazine (50 g) was added. The reaction mixture was heated at about 80 °C for about 3.5 hours, cooled to room temperature and diluted with saturated aqueous $NaHCO_3$ (2 L). The toluene layer was separated and washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to give an oil (754.8 g). Crystallization from methanol/water afforded the desired product as a white solid (609.5 g). ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9H), 2.53 (d, 1H), 2.70 (br s, 2H), 2.88 (br s, 1H), 3.31 (m, 2H), 3.97 (m, 1H), 4.19 (m, 1H), 4.46 (br s, 1H), 4.63 (br s, 1H), 7.06 (m, 2H), 7.51(m, 1H), 8.34 (m, 1H).

C. 3a-Pyridin-2-ylmethyl-2-(2,2,2-trifluoroethyl)-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one

Methanesulfonic acid (11.6 g, 121 mmol) was added dropwise to a solution of the product from step B (10 g, 24.2 mmol) in CH_2Cl_2 (100 mL) over about 30 minutes. The reaction mixture was stirred for about 1 hour, then cooled to about 0 °C, and then triethylamine (18.6 mL, 133.1 mmol) was added through an addition funnel. The mixture was allowed to warm to room temperature over about 1 hour, diluted with additional CH_2Cl_2 and washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the product as a white solid (7.2 g). ^{1}H-NMR ($CDCl_3$) δ: 2.51-2.72 (m, 4H), 3.35 (m, 2H), 3.49 (m, 2H), 4.03 (m, 1H), 4.25 (m, 1H), 7.08 (d, 2H), 7.51 (t, 1H), 8.37 (d, 1H).

D. 3a-Pyridin-2-ylmethyl-2-(2,2,2-trifluoroethyl)-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one (D)-tartrate

In a dry and nitrogen purged 5 L round bottom flask equipped with a mechanical stirrer, D-(-) tartaric acid (129 g, 0.86 mol) was added to the

compound made according to step C (243 g, 0.78 mol) in acetone/water (9:1, 2430 mL) at about 17 °C. The mixture was stirred at room t mperature ov might, filtered, the solid was collected and washed with cold acetone and dried under vacuum. The product was obtained as a yellow solid (284 g, yield 78.8%).

E. 2-*tert*-Butoxycarbonylamino-3-(2,4-difluoro-benzyloxy)-propionic acid

To a solution of N-Boc-(D)-serine (452 g, 2.2026 mol) in a mixture of THF (7 L) and DMF (3 L) at about 0 °C was added potassium *tert*-butoxide solution (515.8 g, 4.5963 mol). The reaction mixture was stirred at about 0 °C for about 30 min., then 2,4-difluorobenzyl bromide (456.5 g, 2.2051 mol) was added. After warming to room temperature, the reaction mixture was concentrated *in vacuo* to remove the THF. Partitioned the reaction mixture between 4.5 L H_2O and 4.5 L IPE. Separated the layers and adjusted the pH of the aqueous layer with 1 N HCl to about 3. The aqueous layer was extracted twice with 4 L each of IPE. The organic solution was dried over Na_2SO_4, and concentrated *in vacuo* to yield a yellow waxy solid (518.0 g, yield: 70.9 %). ^{1}H-NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.73 (m, 1H), 3.94 (d, 1H), 4.44 (br s, 1H), 4.54 (s, 2H), 5.34 (m, 1H), 6.78 (m, 1H), 6.84 (m, 1H), 7.30 (m, 1H).

F. 2-Amino-3-(2,4-difluoro-benzyloxy)-propionic acid, methanesulfonic acid salt

To a solution of the product from step E (1.19 g, 3.59 mmol) in CH_2Cl_2/ IPE (1:1, 12 mL) was added methanesulfonic acid (1.72 g, 17.95 mmol) through a syringe over about 10 minutes. A solid immediately precipitated out of solution. After about 1 hour, the solid was filtered and washed with a CH_2Cl_2/IPE mixture (1:1) to afford 939 mg of product (yield 80 %).

G. 2-(2-*tert*-Butoxycarbonylamino-2-methyl-propionylamino)-3-(2,4-difluoro-benzyloxy)-propionic acid

To a solution of the product from step F (520 mg, 1.46 mmol) in THF/water (4:1, 10 mL) was added 2-*tert*-butoxycarbonylamino-2-methyl-propionic acid-2,5-dioxo-pyrrolidin-1-yl ester (438 mg, 1.46 mmol) and triethylamine (369 mg, 3.65 mmol). The reaction mixture was stirred at room temperature for about 1 hour and quenched with a 10% aqueous citric acid solution (10 mL). After about 15 min., ethyl acetate (50 mL) was added and the organic layer was separated and washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to

give a foam (534.1 mg, yield 88 %). ^{1}H-NMR (CD_3OD): δ 1.38 (br s, 15H), 3.77 (d, 1H), 3.92 (d, 1H), 4.52 (m, 3H), 6.92 (m, 1H), 7.41 (m, 1H), 7.58 (d, 1H).

H. (1-{1-(2,4-Difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethylcarbamoyl}-1-methyl-ethyl)-carbamic acid *tert*-butyl ester

(a) To the compound made according to step D (517 g, 1.12 mol) was added at about -6 °C to ethyl acetate (5170 mL) in a dry and nitrogen purged 12 L round bottom flask equipped with a mechanical stirrer. The solution was cooled to about -40 °C, then triethylamine (398 mL, 2.86 mol) was added over about 45 minutes. The reaction mixture was stirred for about 90 min. at a temperature between about -50 °C and about -40 °C, filtered into a 22 L round bottom flask purged with nitrogen and washed with ethyl acetate (2068 mL, pre-cooled to about -50 °C) to give the free base as a white solid.

(b) The compound made according to step G (425 g, 1.02 mol) was added at about -30 °C to an ethyl acetate solution containing the product from step H(a), triethylamine (654 mL, 4.69 mol) and PPAA (1-propanephosphonic acid cyclic anhydride) (50% in ethyl acetate, 916 mL, 1.53 mol). The reaction mixture was stirred for about 1 hour, washed with water and saturated aqueous NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to give the product as an oil (636 g, yield: 87.8%).

I. 2-Amino-N-{1-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide

Methanesulfonic acid (258.3 mL, 3.98 mol) was added dropwise at about 15 °C over about 55 minutes to the product from step H (566 g, 0.796 mol) in CH_2Cl_2 (11,320 mL) in a dry and nitrogen purged 22 L round bottom flask equipped with a mechanical stirrer. The mixture was stirred for about 40 minutes at about 20 °C, then saturated aqueous $NaHCO_3$ (8,490 mL) was added until the pH was about 7.8. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo* to afford an oily product (388.8 g, yield 80%).

J. 2-Amino-N-[1-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl]-2-methyl-propionamide L-(+) tartrate

To a solution of the product from step I (370 g, 0.6 mol) in methanol (4,070 mL) in a 12 L round bottom flask equipped with a mechanical stirrer was added L-(+) tartaric acid (90 g, 0.6 mol). The reaction mixture was stirred for about 90 min. at about 22 °C, filtered and concentrated. The crude residue was diluted with ethyl acetate (4,560 mL), heated at about 70 °C and slowly allowed to cool to room temperature over about 17 hours. The solid was filtered and dried to give white crystals, mp 188-189 °C (348.46 g, yield 76%). ^{1}H NMR (MeOH, d4) δ: 8.28 (d, 1H), 7.59 (t, 1H), 7.41-7.39 (m, 1H), 7.18-7.13 (m, 1H), 6.92 (t, 1H), 5.2 (t, 1H), 4.56 (bs, 3H), 4.36 (s, 2H), 4.31-4.25 (m, 1H), 4.13-4.06 (m, 1H), 3.78 (d, 2H), 3.21 (t, 1H), 3.18-2.96 (m, 2H), 2.65-2.55 (m, 2H), 1.57 (d, 6H). MS: MH+ 611. $[a]^{589}$ +22.03 (c=11.9, MeOH).

The following assay can be used to show that the combination and methods of this invention increases lean body mass and decreases fat body mass whereas the GH secretagogue alone would be expected to decrease fat body mass with no change in lean body mass and the SERM alone would be expected to increase both lean and fat body mass. Further, the combination increases bone density and decreases total serum cholesterol.

Example Two

Female S-D rats (Harlan) are sham-operated or ovariectomized (OVX) at 3.5 months of age. Drug administration starts when the rats are 9 months of age and 5.5 months post-surgery. The sham-operated rats receive daily gavage of vehicle (10% ethanol in water), while the OVX rats receive daily gavage of vehicle, or 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide at 5 mg/kg/d alone, or (-)cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol at 0.1 mg/kg/d alone, or co-treatment of 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide and (-)cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol for 4 weeks.

In the combination group, 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide is given 2 hours prior to (-)cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol. There are 8 to 10 rats per each subgroup. All rats are given subcutaneous injections with 10 mg/kg of calcein (Sigma Chemical Co., St. Louis, MO) on 13 and 3 days before autopsy. It will be recognized by those skilled in the art that the compounds used in this assay may be administered in the form of a pharmaceutically acceptable salt and that the dosage amount can be readily determined by calculation of the molecular weight of the salt form and performing simple ratios.

Before autopsy on the terminal day of the assay, all rats under ketamine/xylazine anesthesia undergo dual-energy X-ray absorptiometry (DXA, QDR-1000/W, Hologic Inc., Waltham, MA) equipped with Rat Whole Body Scan software (Hologic Inc., Waltham, MA) for lean and fat body mass determination. The rats are then autopsied and blood is obtained by cardiac puncture. Total serum cholesterol is determined using a high performance cholesterol colorometic assay (Boehringer Mannheim Biochemicals, Indianapolis, IN). The body weight gain is calculated as body weight at autopsy minus body weight at day 0. The uterine wet weight is determined immediately at autopsy.

The right femur from each rat is removed at autopsy and scanned using dual energy x-ray absorptiometry (DXA, QDR 1000/W, Hologic Inc., Waltham, MA) equipped with "Regional High Resolution Scan" software (Hologic Inc., Waltham, MA). The scan field size is 5.08 x 1.902 cm, resolution is 0.0254 x 0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and total femoral bone area, bone mineral content, and bone mineral density are determined according to the method described in H. Z. Ke et al., Droloxifene, a New Estrogen Antagonist/Agonist, Prevents Bone Loss in Ovariectomized Rats. ENDOCRINOLOGY 136;2435-2441, 1995.

It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

CLAIMS

1. A pharmaceutical composition comprising:

a. a first compound, said first compound being (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof; and

b. a second compound, said second compound being 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition of claim 1 additionally comprising a pharmaceutical carrier.

3. A pharmaceutical composition of claim 1 wherein said first compound is (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol D-tartrate and said second compound is 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate.

4. A method for treating a mammal suffering from musculoskeletal frailty comprising administering to said mammal a pharmaceutical composition of claim 1.

5. A method of claim 4 wherein said first compound is (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol D-tartrate and said second compound is 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate.

6. A method of claim 4 wherein said mammal is suffering from osteoporosis.

7. A method of claim 4 wherein said mammal is suffering from osteotomy, childhood idiopathic bone or bone loss associated with periodontitis.

8. The method of claim 4 wherein bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction is treated,

vertebral synostosis is induced or long bone extension is enhanced, the healing rate of a bone graft is enhanced or prosthetic ingrowth is enhanced.

9. The method of claim 8 wherein a bone fracture is treated in a human.

10. A method of claim 6 wherein osteoporosis is treated in a human.

11. A method for treating a mammal suffering from musculoskeletal frailty comprising administering to said mammal

a. a first compound, said first compound being (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof; and

b. a second compound, said second compound being 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof.

12. A method of claim 11wherein the first compound and the second compound are administered substantially simultaneously.

13. A method of claim 11 wherein the second compound is administered for a period of from about three months to about three years.

14. A method of claim 13 followed by administration of the first compound for a period of from about three months to about three years without the administration of the second compound during the period of from about three months to about three years.

15. A method of claim 13 followed by administration of the first compound for a period greater than about three years without the administration of the second compound during the greater than about three year period.

16. A method of claim 11 wherein said mammal is suffering from osteoporosis.

17. A method of claim 11 wherein said mammal is suffering from osteotomy, childhood idiopathic bone loss or bone loss associated with periodontitis.

18. The method of claim 11 wherein bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction is treated,

vertebral synostosis is induced or long bone extension is enhanced, the healing rate of a bone graft is enhanced or prosthetic ingrowth is enhanced.

19. The method of claim 18 wherein a bone fracture is treated in a human.

20. A method for increasing muscle mass in a mammal in need thereof comprising administering to said mammal a muscle mass increasing effective amount of a composition of claim 1.

21. A kit comprising:

a. (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and

c. a container.

22. A kit of claim 21 wherein said first unit dosage form comprises (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol D-tartrate and said second unit dosage form comprises 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate.

23. Use of a pharmaceutical composition of claim 1 to prepare a medicament for treating a mammal suffering from musculoskeletal frailty.

24. A use of claim 23 wherein said first compound is (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol D-tartrate and said second compound is 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide L-tartrate.

25. A use of claim 23 wherein said mammal is suffering from osteoporosis.

26. A use of claim 23 wherein said mammal is suffering from osteotomy, childhood idiopathic bone or bone loss associated with periodontitis.

27. The use of claim 23 wherein bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction is treated, vertebral synostosis is induced or long bone extension is enhanced, the healing rate of a bone graft is enhanced or prosthetic ingrowth is enhanced.

28. The use of claim 27 wherein a bone fracture is treated in a human.

29. A use of claim 25 wherein osteoporosis is treated in a human.